REMARKS

The amendments to the claims herein are supported by the as-filed application. No new matter has been added.

Each of claims 2-3 and 33-48 were rejected in a Final Office Action mailed June 5, 2002 ("Final Office Action") under the second paragraph of 35 U.S.C. § 112 and 35 U.S.C. § 103(a), which rejections were maintained in an Advisory Action mailed September 20, 2002 ("Advisory Action"). Applicants have herein amended claims 2, 33, 35, 37, 40, 43, and 46 and added new claims 49-50, and, after careful consideration of the teachings of the references cited in the Final Office Action, applicants respectfully submit that claims 2-3 and 33-50 recite subject matter that is novel and nonobvious in light of the references cited in the Final Office Action.

Claims 1 and 9-11

It was indicated in the Final Office Action that claims 1 and 9-11 remain pending in the application. (Final Office Action, page 3). Applicants respectfully direct the Office's attention to the "VERSION WITH MARKINGS TO SHOW CHANGES MADE" submitted with the Amendment filed herein on February 28, 2002, where cancellation of claims 1 and 9-11 was requested. To the extent said amendment was not effective to cancel claims 1 and 9-11, applicants kindly request the Office to cancel claims 1 and 9-11 without prejudice or disclaimer.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2-3 and 33-48 were rejected under the second paragraph of Section 112 as assertedly being indefinite. Specifically, the Office thought the subject claims vague and indefinite in that there is no clear definition provided in the specification as to what the term "N-terminus" encompasses. Applicants herein have amended claims 2, 33, 35, 37, 40, 43, and 46 to recite that the part of the fiber region of the second serotype is fused to the tail region of the native, or first, serotype, without any reference to "N-terminus".

Rejection under 35 U.S.C. § 103(a) over Crystal *et al.* in view of Wickham *et al.*

Claims 2-3 and 33-48 were newly rejected in the Final Office Action under 35 U.S.C. § 103(a) as being unpatentable over Crystal *et al.* (U.S. Patent 6,127,525)("Crystal") in view of

Wickham *et al.* (U.S. Patent 5,770,442)("Wickham"). Applicants respectfully traverse the rejection for the reasons set forth below.

The Proposed Combination Does Not Teach All Claim Limitations

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); *see also* M.P.E.P. § 702.02(j), 2143. All words in a claim must be considered in judging the patentability of that claim against the prior art. In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants respectfully submit the proposed combination fails to teach or suggest each and every limitation of the subject claims and, accordingly, fails to render the subject claims obvious. Applicants respectfully disagree with the Office's assertion that Crystal anticipates making chimeric fiber proteins. On the contrary, applicants respectfully submit that Crystal's express teachings are limited to complete fiber substitution (*i.e.*, Crystal's "5 base/7 fiber" vector (*See* Crystal, Example 2 at col. 23, line 60 through col. 24, line 54)), resulting in a chimeric ***capsid*** but not a chimeric ***fiber*** protein, as recited in the subject claims.

In the Advisory Action, the Office argued that "Crystal et al clearly contemplate embodiments where the second adenoviral fiber is obtained from those adenoviral serotypes recited in the rejected claims," (Advisory Action, page 2), and that Crystal et al. teach generally that "preferably the fiber protein can be replaced in its entirety, or in part, with sequences of a fiber protein from a different serotype of adenovirus." (Advisory Action, page 3 (quoting Crystal, col. 11, lines 56-59)). However, applicants respectfully point out that Crystal is devoid of any express or inherent teaching of a chimeric fiber protein comprising ***the tail region*** of the native fiber fused to a part of a fiber from a second serotype selected from the serotypes recited in the rejected claims. Crystal's teaching at col. 11, lines 56-59, that the fiber protein can be replaced "in part" with sequences of a different serotype fiber protein is neither expressly nor inherently the same as the limitation of the rejected claims reciting retention of ***the native tail region*** and fusion thereof to a part of a fiber from the recited serotypes.

Applicants agree with the Office that Crystal fails to teach a fusion fiber protein wherein the tail region of the fiber of the native, or first, serotype is retained and fused to the part of the non-native fiber, as recited in the subject claims. (Final Office Action, page 5). Assuming, without conceding, that Crystal does teach true chimeric fiber proteins (*i.e.*, partial fiber swaps as opposed to complete fiber substitution), the Office has identified no part of Crystal teaching chimeric fiber proteins comprising ***the tail region*** of the native fiber fused to a part of a fiber from a second serotype selected from the serotypes recited in the rejected claims. Accordingly, as the Office has acknowledged, Crystal does not teach all the limitations of the rejected claims.

The addition of the teachings of Wickham does not cure the failure of the proposed combination to teach each and every limitation of the subject claims. Wickham's teachings with respect to fiber chimeras in which the amino-terminal region of the native fiber is retained and operatively linked to the tropism-determining region of a fiber of another serotype are limited to the Ad5/Ad2 chimera of Example 1 and the Ad5/Ad3 chimera of Example 2. (Wickham, col. 11, line 43 through col. 12, line 62).

The evidence of record in this case establishes that the Ad5/Ad2 and Ad5/Ad3 chimeras disclosed in Wickham are far inferior to the fiber chimeras of the claimed invention due to the extremely high antigenicity of adenovirus serotypes 2 and 3 and the comparatively lower antigenicities of the adenovirus serotypes recited in the claims 2-3 and 33-50, namely, serotypes 11, 14, 16, 21, 34, 35, and 50. Applicants respectfully direct the Office's attention to the Declaration under 37 C.F.R. § 1.132 of Menzo Havenga, Ph.D., filed herein on August 1, 2000 ("Havenga Declaration I") (*see, e.g.*, Havenga Declaration I, page 5; FIG. 1). That is, adenovirus serotypes 2 and 3, the fibers Wickham et al. used to create their Ad5/Ad2 and Ad5/Ad3 chimeras, were neutralized in 92% and 93% of human sera. (Havenga Declaration I, FIG. 1). On the other hand, adenovirus serotypes 11, 14, 16, 21, 34, 35, and 50 were only neutralized in 0%, 0%, 37%, 44%, 5%, 0%, and 39%, respectively. (Id.). It thus can be seen that the fiber chimeras claimed in claims 2-3 and 33-50 are substantially lower in antigenicity, and therefore substantially better suited to gene transfer vectors, than the fiber chimeras disclosed in Wickham.

Enclosed herewith is the Declaration under 37 C.F.R. § 1.132 of Menzo Havenga, Ph.D., dated January 3, 2003 ("Havenga Declaration II"). As set forth in the Havenga Declaration II, the chimeric adenoviruses of the present invention, which comprise the tail region of a native

fiber fused to a part of a fiber of a nonnative serotype, are less antigenic than wild-type adenovirus serotype 5 and are expected to be more stable than chimeric adenoviruses such as those taught by Crystal. (Havenga Declaration II, FIGS. 1-4).

With respect to vector stability in Crystal's "5 base/7 fiber" vector, there is only approximately 57% amino acid sequence homology between the tail regions of fibers from Ad5 and Ad7. (Gall *et al.* (1996), "Adenovirus Type 5 and 7 Capsid Chimera: Fiber Replacement Alters Receptor Tropism without Affecting Primary Immune Neutralization Epitopes," Journal of Virology, vol. 70: no. 4, pp. 2116-2123, *see, e.g.,* FIG. 1 (cited by the Office in the Office Action mailed February 1, 2000) ("Gall (1996)")). Furthermore, Gall (1996) teaches that the receptor for Ad5 and Ad7 is the same, but that the lack of expression in the secondary sites of infection might be due to "an inherent instability of the chimeric virus". (Gall (1996), p. 2121, 2nd col., lines 8-12).

Given the substantial difference in structure between the tail regions of the Ad5 and Ad7 fibers as taught by Gall (1996), the interaction between the Ad5 penton-base and the Ad7 fiber tail region in Crystal's "5 base/7 fiber" vector is expected to be less stable than if the Ad5 fiber tail region were retained. The expected stability of the chimeric adenoviruses of the present invention is due to the retention of the native fiber tail region, which ensures proper interaction between the fiber and the penton-base. (Havenga Declaration II, FIG. 4).

Each of claims 2-3 and 33-50 specifies the particular adenovirus serotype(s) from which the non-native part of each fiber chimera is obtained, none of which includes serotypes 2 or 3, as disclosed in Wickham. To wit: claims 2, 3, 33, 34, 37, and 43-45 each recite that the non-native part of the fiber chimera is from a serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50, and claims 35, 36, 38-42, and 46-50 each recite that the non-native part of the fiber chimera is from serotype 35. The proposed combination of Crystal and Wickham advanced by the Office fails to teach or suggest this limitation of the subject claims and, accordingly, the Office has not established a *prima facie* case of obviousness with respect to the subject claims.

Assuming, without conceding, that Crystal does teach true chimeric fibers (*i.e.*, partial fiber swaps as opposed to complete fiber substitution) and that Crystal's chimeric fibers can include parts of fibers from serotypes 11, 14, 16, 21, 34, and 35 (but not 50), Crystal still fails to

expressly or inherently disclose retention of ***the tail region*** of the native fiber and fusion thereof to a part of a fiber from the serotypes recited in claims 2-3 and 33-50. Further, although Wickham discloses fiber chimeras in which the Ad5 fiber receptor binding domain is switched for an Ad2 or Ad3 receptor binding domain (*see* Wickham, Examples 1-2 (col. 11, line 42 through col. 12, line 62)), Wickham's fiber chimeras are inferior to the claimed fiber chimeras due to the extremely high antigenicity of serotypes 2 and 3. (*See*, Havenga Declaration I, FIG. 1). Thus, the proposed combination of Crystal and Wickham fails to teach each and every limitation of claims 2-3 and 33-50. Applicants therefore respectfully solicit withdrawal of the rejection on this basis.

Lack of Motivation to Combine Reference Teachings

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. In re Lee, 277 F.3d 1338, 1343, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002); *see also* In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000); In re Fine, 5 USPQ2d at 1596; In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The Office must make particular findings as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. In re Lee, 277 F.3d at 1343. These findings must extend to all material facts and must be documented on the record. Id. at 1345.

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993); *see also* In re Kotzab, 217 F.3d at 1371; Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 1324, 50 USPQ2d 1161, 1171 (Fed. Cir. 1999).

The teaching or suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Office has not identified any proper suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or combine reference teachings. When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. In re Lee, 277 F.3d at 1343. The Office must make particular findings as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. Id. at 1343. These findings must extend to all material facts and must be documented on the record. Id. at 1345.

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. Ex parte Levengood, 28 USPQ2d at 1300 ; *see also* In re Kotzab, 217 F.3d at 1371; Al-Site Corp., 174 F.3d at1324.

In response to applicants' argument in the Amendment filed herein on August 21, 2002, that the Office failed to establish the requisite suggestion or motivation to combine the teachings of Crystal and Wickham to produce the claimed invention, it is stated in the Advisory Action:

> "Crystal et al make clear that ***it is possible*** to construct adenoviral vector having chimeric hexon proteins and chimeric fiber proteins for the purpose of constructing a vector that is not as antigenic as a 'wildtype' adenoviral vector lacking the nonnative sequences in the adenoviral hexon or fiber. Wickham et al make clear that ***it is within the skill of the art*** for one to construct and use an adenoviral gene transfer vector that comprises a chimeric fiber protein such that the tropism of the adenoviral vector is altered to a desired cell type displaying a particular receptor that binds the chimeric fiber. The adenoviral vectors taught by Crystal et al and Wickham et al are both involved in the transfer of a desired gene to a cell of a desired trait and are analogous in function. One of ordinary skill in the art and aware of the teachings of Crystal et al and Wickham et al ***would readily recognize the advantages*** of having an adenoviral gene transfer vector that has 1) decreased antigenicity (as taught by Crystal et al) and 2) tropism for a desired cell type (as taught by Wickham et al). Absent any evidence to the contrary, and in contradiction to the assertion that the rational for combination of the two references is merely an 'obvious-to-try' motivation, there would have been a ***reasonable expectation of combining the teachings of Crystal et al and***

> ***Wickham et al*** to construct and use an adenoviral vector having decreased antigenicity (e.g. an altered hexon protein as taught by Crystal et al) and altered tropism (e.g. an altered receptor binding domain as taught by Wickham et al). Applicants have provided no indication as to why such an adenoviral vector could not be constructed and why it would not work." (Advisory Action, pages 3-4 (emphasis added)).

The Office has not identified any prior art of record that teaches or suggests the selection and combination of the teachings of Crystal and Wickham as proposed by the Office. As evidenced by the above-quoted language from the Advisory Action, it is apparent the Office is relying on the level of skill in the art to provide the requisite suggestion or motivation to select and combine Crystal and Wickham as proposed. However, established precedent holds that the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *See, e.g.,* Ex parte Levengood, 28 USPQ2d at 1300; In re Kotzab, 217 F.3d at 1371; Al-Site Corp. v. VSI Int'l Inc., 174 F.3d at 1324; *see also* M.P.E.P. § 2143.01. Therefore, the Office's reliance on the level of skill in the art to provide the requisite suggestion to combine Crystal and Wickham is not a proper basis for *prima facie* obviousness.

In addition, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 682 (Fed. Cir. 1990); In re Fritch, 972 F.2d 1260 (Fed. Cir. 1992); *see also* M.P.E.P. § 2143.01. The statement at page 4 of the Advisory Action that "[o]ne of ordinary skill in the art and aware of the teachings of Crystal et al and Wickham et al ***would readily recognize the advantages*** of having an adenoviral gene transfer vector that has 1) decreased antigenicity (as taught by Crystal et al) and 2) tropism for a desired cell type (as taught by Wickham et al)" is simply a recognition that the teachings of Crystal and Wickham can be combined, but the Office has not shown where the cited prior art suggests the desirability of the proposed combination.

The statement at page 4 of the Advisory Action that "there would have been a ***reasonable expectation of combining the teachings of Crystal et al and Wickham et al*** to construct and use an adenoviral vector having decreased antigenicity (e.g. an altered hexon protein as taught by Crystal et al) and altered tropism (e.g. an altered receptor binding domain as taught by Wickham et al)" likewise fails to support *prima facie* obviousness. Even if there is a reasonable expectation of success in combining reference teachings, the Office nevertheless must show a

teaching, suggestion, or motivation in the cited references that would lead an ordinarily skilled artisan to select and combine reference teachings. *See* In re Lee, 277 F.3d at 1434-1345.

Furthermore, applicants respectfully submit that Crystal teaches away from adenoviruses comprising chimeric fibers without other capsid modifications, as in the claimed invention. To wit, Crystal states:

> "switching the fiber from that of adenoviral serotype 5 group C vector to that of an adenoviral serotype 7 group B vector by itself is insufficient to allow the vector to escape neutralizing antibodies generated against an adenoviral vector comprising Ad5 fiber. These results imply that antibodies against adenoviral structures other than fiber also are important in the process of neutralizing immunity. Furthermore, whereas switching the fiber serotype to another serotype may be insufficient in and of itself to allow an adenovirus to escape immune detection, such switching when done in combination with removal of other epitopes may be desirable, for instance, to reduce an immune response." (Crystal, col. 25, lines 15-27).

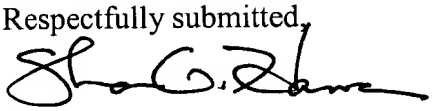
Crystal thus teaches that effective reduction in immune response cannot be accomplished with fiber mutagenesis alone but, rather, that mutagenesis of other capsid proteins is also necessary. Crystal notably fails to teach or suggest that selecting fibers from other non-neutralized serotypes (*i.e.*, other than Ad7), as in the claimed invention, could result in reduced immune response. Accordingly, the teachings of Crystal would have led one of ordinary skill in the art at the time of the present invention to avoid generating chimeric adenoviruses having chimeric fiber proteins without modifications to other capsid proteins, as recited in the rejected claims.

The Office has not documented on the record any teaching, motivation, or suggestion in the cited prior art to select and combine Crystal and Wickham in the manner proposed by the Office. Id. Neither Crystal nor Wickham suggest the desirability of combining each other's teachings, nor is there any other evidence of record to provide the requisite suggestion or motivation to select and combine Crystal and Wickham in the manner proposed. Indeed, as discussed above, Crystal teaches away from the claimed invention because Crystal teaches that it is necessary to modify other epitopes, not just the fiber. Accordingly, applicants respectfully submit the Office has not established *prima facie* obviousness and respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Claims 2, 3, and 33-50 are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. If questions should remain after consideration of the foregoing that might be resolved by a telephone interview, the Office is kindly requested to contact applicants' attorney of record, whose telephone number is (801) 532-1922.

Respectfully submitted,



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DATED: January 6, 2003
SGH/le
Enclosure: VERSION WITH MARKINGS TO SHOW CHANGES MADE; and
Declaration under 37 C.F.R. § 1.132 of Menzo Havenga, Ph.D., dated January 3, 2003 ("Havenga Declaration II")

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

2. (Six Times Amended) A recombinant vector derived from an adenovirus comprising at least one ITR and a packaging signal, the recombinant vector having a first insertion site for a nucleic acid sequence of interest, a second insertion site for functionally inserting a gene sequence encoding at least a part of a penton and/or hexon protein of a first adenovirus serotype, and a third insertion site for a gene sequence encoding a part of a fiber protein of a second adenovirus serotype, the second adenovirus serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50, a gene sequence encoding at least a part of a penton and/or hexon protein from the first adenovirus serotype inserted into the second insertion site, a gene sequence encoding the part of a fiber protein of the second adenovirus serotype inserted into the third insertion site, the gene sequence encoding the part of a fiber protein adapted to exhibit a desired tropism to a plurality of target cells in a host and fused to a tail region of a fiber of the adenovirus serotype from which the recombinant vector was derived[at its N-terminus].

33. (Twice Amended) A chimeric adenovirus comprising:

an adenoviral capsid derived from a first adenovirus serotype; and

a part of an adenoviral fiber derived from a second adenovirus serotype substituted for a corresponding part of a fiber of the capsid derived from the first adenovirus serotype, the second adenovirus serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50, wherein the part of the adenoviral fiber derived from the second adenovirus serotype is fused to a tail region of a fiber of the first adenovirus serotype[at its N-terminus].

35. (Twice Amended) A chimeric adenovirus comprising:

an adenoviral capsid derived from a first adenovirus serotype; and

a part of an adenoviral fiber derived from adenovirus serotype 35 substituted for a corresponding part of a fiber of the capsid derived from the first adenovirus serotype, the part of the adenoviral fiber derived from adenovirus serotype 35 fused to a tail region of a fiber of the first adenovirus serotype[at its N-terminus].

37. (Twice Amended) A method for producing a chimeric adenoviral particle having a capsid derived from a first adenovirus serotype exhibiting a desired tropism and antigenicity determined by a part of a fiber of a second adenovirus serotype, the second adenovirus serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50, the method comprising:

providing a recombinant vector derived from the first adenovirus serotype comprising at least one ITR, a packaging signal, an insertion site for a nucleic acid sequence of interest, and an insertion site for a gene sequence encoding a functional part of a fiber protein of the second adenovirus serotype;

inserting into the recombinant vector the gene sequence encoding the functional part of the fiber protein of the second adenovirus serotype, wherein the functional part of the fiber protein of the second adenovirus serotype is fused to a tail region of a fiber of the first adenovirus serotype[at its N-terminus];

transfecting said vector in a packaging cell; and

producing chimeric adenoviral particles.

40. (Twice Amended) A method for producing a chimeric adenoviral particle having a capsid derived from a first adenovirus serotype exhibiting a desired tropism and antigenicity determined by a part of a fiber derived from adenovirus serotype 35, the method comprising:

providing a recombinant vector derived from the first adenovirus serotype comprising at least one ITR, a packaging signal, an insertion site for a nucleic acid sequence of interest, and an insertion site for a gene sequence encoding a functional part of the fiber protein of adenovirus serotype 35;

inserting into the vector the gene sequence encoding the functional part of the fiber protein derived from adenovirus serotype 35, wherein the functional part of the fiber protein of the second adenovirus serotype is fused to a tail region of a fiber of the first adenovirus serotype[at its N-terminus];

transfecting said vector in a packaging cell; and

producing chimeric viral particles.

43. (Twice Amended) A recombinant vector derived from a first adenovirus serotype comprising:

at least one ITR;

a packaging signal;

a first insertion site for a nucleic acid sequence of interest;

a second insertion site for functionally inserting a gene sequence encoding a part of a fiber protein of a second adenovirus serotype, the second adenovirus serotype selected from the group consisting of serotypes 11, 14, 16, 21, 34, 35, and 50; and

a gene sequence encoding the part of the fiber protein of the second adenovirus serotype inserted in the second insertion site, the part of the fiber protein of the second adenovirus serotype exhibiting a desired tropism to a plurality of cells in a host and fused to a tail region of a fiber of the first adenovirus serotype[at its N-terminus].

46. (Twice Amended) A recombinant vector derived from a first adenovirus serotype comprising:

at least one ITR;

a packaging signal;

a first insertion site for a nucleic acid sequence of interest;

a second insertion site for functionally inserting a gene sequence encoding a part of a fiber protein of adenovirus serotype 35; and

a gene sequence encoding the part of the fiber protein of adenovirus serotype 35 inserted in the second insertion site, the part of the fiber protein of adenovirus serotype 35 exhibiting a desired tropism to a plurality of cells in a host and fused to a tail region of a fiber of the first adenovirus serotype[at its N-terminus].